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Optically Active Transition Metal Complexes. 87.** Synthesis of Porphyrin Complexes Containing Chiral Fe Atoms. Demonstration of Fe Chirality by ^{1}H NMR Spectroscopy

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After transformation of the vinyl groups in hemin into H, CH_2CH_3 and $COCH_3$, the propionic acid side chains were converted into esters and amides using (−)-menthol, (−)-2-methylbutanol and (−)-1-phenylethylamine. By introducing the CS ligand into the apical position, square pyramidal complexes were obtained, differing only in the Fe configuration, which could not be separated. However, the two diastereomers with different Fe configuration, having optically active 1-phenylethylisonitrile and pyridine (or 4-methylpyridine) as ligands in the axial positions, at −20 °C exhibit different chemical shifts demonstrating configurational stability at the Fe atom on the ^{1}H NMR time scale. At room temperature epimerization at the Fe atom occurs by ligand exchange reactions.

Introduction

The unsubstituted porphyrin dianion belongs to point group D_{4h}, containing besides the proper rotation axes one horizontal and four vertical symmetry planes, an inversion center, and one fourfold improper axis. The porphyrin skeletons of octaethylporphyrin and mesotetraphenylporphyrin, frequently used in porphyrin studies, have the same symmetry properties. However, the substitution pattern of natural protoporphyrin IX is such that as the only element of symmetry a plane of symmetry (the plane of the molecule) is left. The same symmetry arguments hold for metal complexes of protoporphyrin IX with no axial substituents or with two identical substituents. Introduction of only one axial ligand (the other axial position being vacant) or of two different axial ligands in a metal complex of protoporphyrin IX removes the symmetry plane of the porphyrin system making the metal atom a center of chirality. The symmetry arguments given do not change if the labile vinyl groups in protoporphyrin IX are replaced by hydrogen or converted to ethyl and acetyl groups.

In the following we describe the synthesis and characterization of the chiral Fe complexes **3a–e** and **4a,b** containing either one CS ligand or an isonitrile/pyridine combination. Diastereotopic splitting in the ^{1}H nmr spectra of complexes **4a** and **4b** demonstrates the chirality at the Fe atom and its configurational stability on the NMR time scale.

Experimental

All metalloporphyrins were manipulated under an atmosphere of dry oxygen-free nitrogen in dry degassed solvents. IR spectra (KBr pellets) were recorded on a Beckman 4240 spectrometer. ^{1}H NMR spectra were obtained with a Bruker WH 90, Bruker 250 WM or Bruker 400 spectrometer (δ-values).

Hemin 1 was obtained from blood [2]. Its vinyl groups were replaced by hydrogen atoms when 1 was fused with resorcinol at 160 °C for 30 min [3]. Mesoporphyrin was obtained by catalytic hydrogenation of the 2- and 4-vinyl groups with Pd/C in formic acid [4]. Acyl derivatives were prepared by electrophilic substitution reactions from deuteroporphyrins [5]. Esterifications and amidations of the different porphyrins were carried out according to published procedures or modifications of them [6–8]. Removal and insertion of iron in the porphyrin skeleton was effectuated by the ferrous acetate/acetic acid method [9]. *R*-(+)-1-phenyl isonitrile was prepared via the formamide [10, 11].

Synthesis of Complexes 3a–e

All these complexes were prepared in essentially the same manner as described for **3a**. 1 g of the iron(III)–chloride complex of **2a** was dissolved in 200 ml THF. This solution was stirred with 2.3 ml Na/Hg amalgam (1%) for 60 min at room temperature. To this mixture a solution of 1.2 ml thiophosgene in 5 ml THF was added. After stirring 18 h at room

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temperature the excess amalgam was drained off and the resulting solution was concentrated and chromatographed on Al_2O_3 (activity IV) with toluene/ether 1:1 or with THF/ether 1:1 in the case of the amide-derivatives. The red zone was rechromatographed. Crystallization from ether/pentane or THF/ether 1:1 yields a red powder. Yield 50–60%.

(3a) Thiocarbonyl[deuteroporphinato-di(S)-(−)-1-phenylethylamide]iron(II)

M.p. 215 °C (dec.). *Anal.* Found, C, 68.87; H, 5.40; N, 9.92%; Calcd.: C, 69.20; H, 5.68; N, 10.31. IR: ν(NH) 3290, ν(CO) 1643, ν(CS) 1279 cm^{-1}. ^1H nmr (d_7-DMF): 10.77 (s), 10.21 (s), 10.07 (s), 9.14 (s), 9.12 (s), 8.59 (d) [12], 7.00 (m), 5.14 (m), 4.92 (t, J = 7.0 Hz), 3.70 (s), 3.65 (s), 3.58 (s), 3.50 (s), 1.25 (m).

(3b) Thiocarbonyl[deuteroporphinato-di(S)-(−)-2-methylbutylester]iron(II)

M.p. 134–135 °C. *Anal.* Found, C, 67.12; H, 6.63; N, 7.16%; Calcd.: C, 67.44; H, 6.49; N, 7.00. IR: ν(CO) 1728, ν(CS) 1283 cm^{-1}. ^1H nmr ($CDCl_3$): 9.87 (s), 9.82 (s), 9.79 (s), 8.86 (s), 3.93 (m), 3.56 (s), 3.54 (s), 3.49 (s), 3.45 (s), 3.39 (t), 3.21 (t, J = 7.0 Hz), 1.11 (m).

(3c) Thiocarbonyl[mesoporphinato-di(S)-(−)-1-phenylethylamide]iron(II)

M.p. 204–205 °C (dec.). *Anal.* Found, C, 69.15; H, 6.25; N, 9.65%; Calcd.: C, 70.33; H, 6.25; N, 8.83. IR: ν(NH) 3300, ν(CO) 1642, ν(CS) 1285 cm^{-1}. ^1H nmr (d_7-DMF): 10.20 (s), 10.06 (s), 7.10 (m), 5.10 (m), 4.22 (q, J = 7.0 Hz), 4.36 (t, J = 7.0 Hz), 3.60 (s), 3.57 (s), 3.51 (s), 3.45 (s), 3.21 (t, J = 7.0 Hz), 1.74 m, 1.13 (t, J = 7.0 Hz).

(3d) Thiocarbonyl[mesoporphinato-di(−)-menthylester]iron(II)

M.p. 85–86 °C. *Anal.* Found, C, 70.21; H, 7.66; N, 6.01%; Calcd.: C, 70.19; H, 7.71; N, 5.95. IR: ν(CO) 1723, ν(CS) 1287 cm^{-1}. ^1H nmr ($CDCl_3$): 9.95 (s), 9.93 (s), complicated multiplet between 3.10 and 5.00 ppm, menthyl signals between 1.68 and 2.70.

(3e) Thiocarbonyl[diacetyldeuteroporphinato-di-(S)-(−)-2-methylbutylester]iron(II)

M.p. 156–158 °C. *Anal.* Found, C, 67.02; H, 6.31%; Calcd.: C, 67.66; H, 6.56. IR: ν(CO) 1730, ν(CO) 1643, ν(CS) 1281 cm^{-1}. ^1H nmr ($CDCl_3$): 10.58 (s), 9.57 (s), complicated multiplet between 3.10 and 5.15, 1.13 (m).

Synthesis of Complexes 4a–c

All these complexes were prepared in the same manner as described for **4a**. 2 g (3.1 mmol) deuterohemindimethylester were dissolved in 200 ml CH_2Cl_2 and 20 ml CH_3OH. Then, 10 g iron powder and 0.64 g (9 mmol) pyridine were added and the mixture was stirred for 1 h at room temperature. To this mixture 0.4 g (3.1 mmol) *R*-(+)-1-phenylethylisonitrile were added slowly. After stirring for additional 3 h the iron was filtered off. The solvents were removed and the residue was chromatographed twice on Al_2O_3 (activity III) with a 1:1 mixture of benzene/ether as eluent. Crystallization from toluene/pentane 1:1.5 plus 0.4 ml pyridine. The dark red precipitate was collected, washed with pentane and dried. Yield 55%.

(4a) (R)-(+)-1-Phenylethylisonitrile-pyridine-(deuteroporphinato-dimethylester)iron(II)

M.p. 138 °C (dec.). *Anal.* Found C, 68.37; H, 5.61; N, 10.43%; Calcd.: C, 68.82; H, 5.73; N, 10.47. IR: ν(CN) 2105, ν(CO) 1740 cm^{-1}. ^1H nmr (d_8-toluene, −20 °C): 9.94 (s), 9.81 (s), 9.79 (s), 9.69 (s), 9.64 (s), 9.63 (s), 8.86 (s), 8.83 (s), 8.82 (s), 6.60 (m), 4.60 (m), 4.31 (m), 4.11 (t, J = 7.0 Hz), 3.52 (s), 3.46 (s), 3.44 (s), 3.38 (s), 3.35 (s), 3.31 (s), 3.28 (s), 3.20 (m), 3.19 (s), 3.15 (s), 1.69 (d, J = 7.0 Hz), 1.26 (q, J = 7.0 Hz), −1.08 (d, J = 7.0 Hz).

(4b) (R)-(+)-1-Phenylethylisonitrile-(4-methylpyridine)-(deuteroporphinatodimethylester)iron(II)

Prepared similar to **4a** with 4-methylpyridine instead of pyridine. Yield 60%. M.p. 91 °C (dec.). *Anal.* Found, C, 68.70; H, 5.85; N, 10.24; Calcd.: C, 68.91; H, 5.62; N, 10.36; IR: ν(CN) 2102, ν(CO) 1740 cm^{-1}. ^1H nmr (d_8-toluene, −20 °C): 9.95 (s), 9.82 (s), 9.80 (s). 9.71 (s), 9.67 (s), 9.66 (s), 8.89 (s), 8.86 (s), 8.85 (s), 6.65 (m), 4.33 (m), 3.93 (d, J = 7.0 Hz), 3.55 (s), 3.50 (s), 3.49 (s), 3.43 (s), 3.41 (s), 3.36 (s), 3.33 (s), 3.26 (m), 3.24 (s), 1.55 (d, J = 7.0 Hz), 1.29 (q, J = 7.0 Hz), 0.13 (s), −1.06 (d, J = 7.0 Hz).

(4c) Bis[(R)-(+)-1-phenylethylisonitrile](deuteroporphinato-dimethylester)iron(II)

Prepared similar to **4a** without pyridine. Yield 66%. M.p. 84 °C (dec.). *Anal.* Found. C, 70.43; H, 5.75; N, 9.84; Calcd.: C, 70.26; H, 5.90; N, 9.83. ^1H nmr: Fig. 1.

Discussion

Thiocarbonyl Complexes 3a–e

In hemin 1 the Fe atom is an asymmetric center. However, its configuration is extremely labile and the vinyl groups are very reactive. To stabilize the system the metal atom was removed and the vinyl substituents at the porphyrin skeleton were transformed into H, C_2H_5, $COCH_3$. The acids 2 (R′ = OH) were converted into the esters and amides **2a–e**

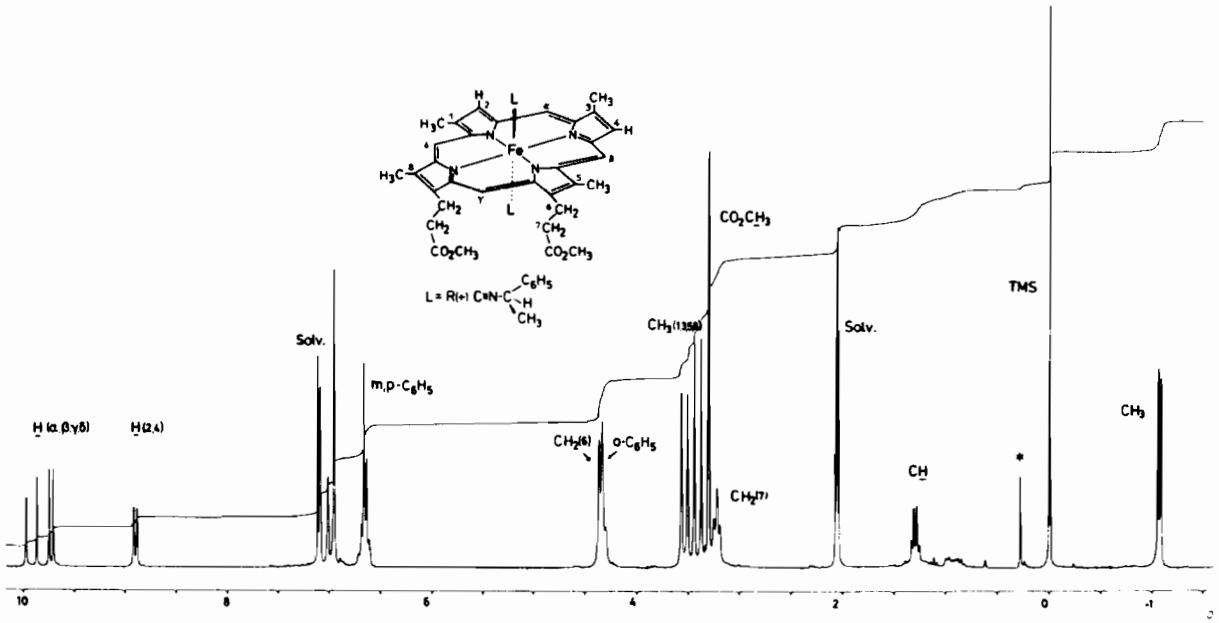
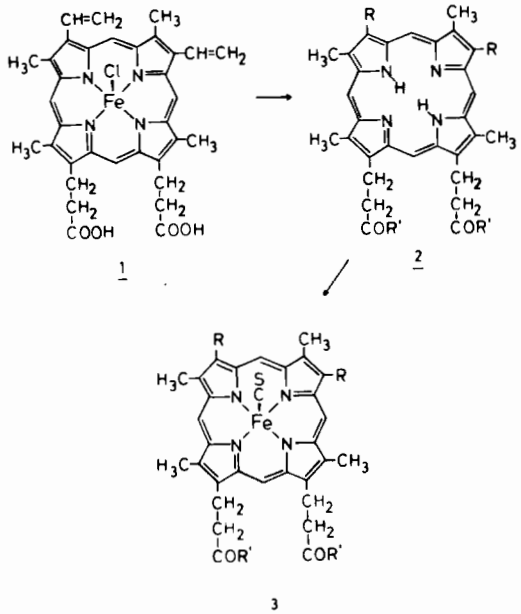


Fig. 1. 250 MHz ^{1}H-NMR spectrum of **4c** in toluene-d_8 at −253 K (i-TMS).



3a: R = H; R' = S(−)-NHCH(CH_3)(C_6H_5)
3b: R = H; R' = S(−)-$OCH_2CH(CH_3)(C_2H_5)$
3c: R = CH_2CH_3; R' = S(−)-NHCH(CH_3)(C_6H_5)
3d: R = CH_2CH_3; R' = (−)-$OC_{10}H_{19}$
3e: R = $COCH_3$; R' = S(−)-$OCH_2CH(CH_3)(C_2H_5)$

Scheme 1.

using the optically active alcohols (−)-menthol, (−)-2-methylbutanol and (−)-1-phenylethylamine. After incorporation of the FeCl moiety reduction to Fe(II) and introduction of the CS ligand was carried out by treatment with Na-amalgam and thiophosgene in THF [12–14] to give the stable complexes **2a–e** which consist of pairs of diastereomers differing only in the Fe configuration (Scheme 1). Their analytical, IR and ^{1}H NMR spectroscopic data are summarized in the Experimental Section.

Whereas the solubility of the amides **3a**, **3c** is low the esters **3b**, **3d**, **3e** are readily soluble in all common organic solvents. With all five complexes **3a–e** repeated fractional crystallizations in different solvents were carried out. However, no diastereomer enrichment could be obtained as less and more soluble fractions always showed small and identical optical rotations. Also chromatography on 1 m columns of Al_2O_3 and cellulose, as well as chromatography at 3 successive Merck Lobar columns type B using temperatures down to −70 °C, did not lead to isomer enrichments. Cutting the broad red zone into different parts gave fractions which uniformly showed small and identical optical rotations. The unsuccessful diastereomer separation could be due to the fact that the chiral centers in compounds **3a–e**, located at the Fe atom and in the ester or amide part of the propionic acid side chains, are too far apart from each other. Therefore complexes of type **4** were tested, in which the asymmetric centers are closer together.

Isonitrile Complexes *4a–c*

Hemin 1 was transformed to 2 (R = H, R' = OH) as described above. After conversion into the methyl ester and incorporation of the FeCl moiety reduction was carried out with Fe powder. In the presence of pyridine an intermediate was formed which on addi-

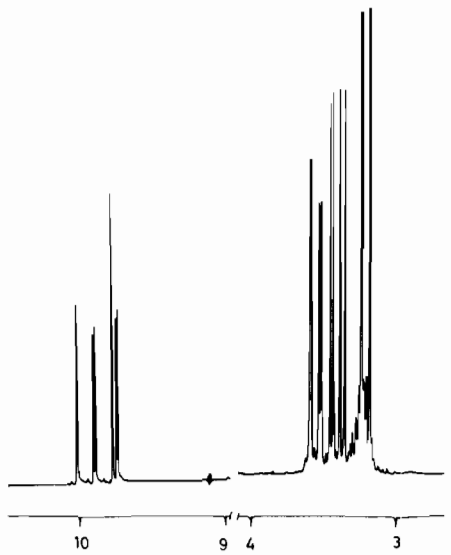
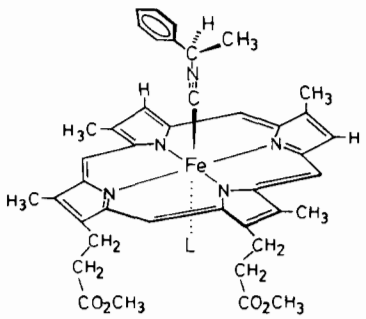


Fig. 2. 400 MHz ^{1}H-NMR spectrum of **4a** in toluene-d_8 at −253 K.

tion of (+)-1-phenylethylisonitrile [15] forms the octahedral complex **4a**, containing one pyridine and one isonitrile ligand. With 4-methylpyridine the corresponding complex **4b** could be obtained (Scheme 2). After addition of (+)-1-phenylethylisonitrile to the reduced solution in the absence of pyridine complex **4c** was formed containing two isonitrile ligands at the axial sites. Such octahedral diisonitrile derivatives have also been described previously [16, 17]. The syntheses, analytical and spectroscopic data for complexes **4a–c** are given in the Experimental Section. In the mass spectra of **4a** and **4b** only phenylethylisonitrile on the one hand and pyridine and methylpyridine on the other were observed.



4a: L = pyridine
4b: L = 4-methylpyridine
4c: L = (*R*)-(+)-phenylethylisonitrile

Scheme 2

The ^{1}H NMR spectrum of **4c** in toluene-d_8 is shown in Fig. 1. The meso protons H($\alpha, \beta, \gamma, \delta$) are well resolved at low field, as are the porphyrin protons H(2,4) and the porphyrin methyl groups (1,3, 5,8). The methylene groups CH_2(6) and CH_2(7) give rise to two multiplets and the methylester groups to two adjacent singlets. The two isonitrile ligands exhibit a quartet and a doublet for the $CHCH_3$ group shifted upfield due to the porphyrin ring current. This effect is also responsible for the high field shift of the ortho-protons of the isonitrile phenyl with respect to the meta- and para-protons, which are further away from the porphyrin plane.

The two diastereomers of the asymmetric complex **4a**, differing only in the Fe configuration, in toluene-d_8 show different chemical shifts (Fig. 2). Two of the meso proton signals, the four porphyrin methyl signals and the two methyl ester signals exhibit diastereomer splitting at −20 °C. At lower temperatures the spectrum does not change. At room temperature, however, the diastereomer splitting disappears because epimerization and ligand exchange with respect to the Fe atom become fast on the NMR time scale. This is also apparent from the signals of **4c** present in the spectrum shown in Fig. 2 on the low field side of the meso proton area and between the large signals in the methyl area. **4c** is absent on dissolving recrystallized samples of **4a** at temperatures below −20 °C, but it appears on warming the solution above −20 °C. The small signals of **4c** in Fig. 2 represent its equilibrium contribution in the ligand exchange equilibrium after dissolution of **4a** at room temperature. These results demonstrate the configurational stability up to −20 °C of the two diastereomers of **4a**, differing only in the Fe configuration, and the occurrence of ligand exchange reactions and equilibria at higher temperatures.

Other isonitriles such as isopropylisonitrile and benzylisonitrile were added to solutions of complex **4a**. In the same temperature range as discussed above ligand exchange reactions took place. The spectra became quite complicated but the meso proton area was especially well resolved. The spectra obtained were compatible with the presence of all the complexes with identical isonitriles, different isonitriles, and isonitrile/pyridine combinations as axial ligands.

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